Remarks

Claims 24, 26, 27, 29-37, 44, 52, 54 and 61-66 are in the case.

Before discussing the rejection, the following discussion of Claim 61 and the applied references is provided.

Claim 61

This claim involves the steps of (a) detecting for one marker in unenriched body fluid, (b) and (c) enriching the body fluid in cancer cells and detecting for a second marker in the enriched body fluid, (d) detecting for the second marker in a normal (non-cancer) cell from the body fluid. The presence of the first marker in unenriched body fluid and detection of increased or decreased presence of second marker in enriched body fluid compared to presence or absence of second marker in a normal (non-cancer) cell from the unenriched or enriched body fluid indicates an increased risk of the presence of disseminated or micrometastasized cancer cells.

Ditkoff

Ditkoff involves detecting for one marker in unenriched body fluid, i.e., equal to step (a) of Claim 61.

Hoon

Hoon involves detecting for two markers in one sample of unenriched body fluid to increase selectivity (increased chance of no false positive) or sensitivity (increased chance of no false negative) compared to Ditkoff (equal to two steps (a) of Claim 61 on one sample).

Schmitz

Schmitz presumes tumor cells share many phenotypic markers with the cell type from which they originate (source; col. 3, lines 52-54), relies upon one such marker for obtaining enriched body fluid and may detect a marker in enriched body fluid (equal to steps (b) and (c) of Claim 61) to increase sensitivity and selectivity compared to Ditkoff for one marker in unenriched body fluid.

Rimm

Rimm presumes cancer cells of epithelial origin have a different density from other nucleated constituents of blood (col. 4, lines 4-7) and may verify presence of cancer cells by detecting a marker in fraction enriched based on density.

We turn now to the rejections.

The claims are rejected under 35 U.S.C. 103(a) as being obvious over the combination of Ditkoff et al, Schmitz et al, Hoon et al. and Rimm et al. The position is that Ditkoff teaches step (a) of Claim 61, Schmitz teaches steps (b) and (c) of Claim 61, Hoon teaches detecting multiple markers for increased sensitivity compared to use of single markers and Rimm teaches the limited benefit of detecting in enriched (and/or unenriched) body fluid (where either detection or enrichment of cancer cells is based on markers that reflect the source of spread; cf. the discussion in Rimm at col. 2, lines 17-58), so it would be obvious to use multiple markers (Hoon), one in step (a) (Ditkoff), a different one in step (c) (Schmitz) because of the limited benefit of detecting only in enriched (and/or unenriched) body fluid (Rimm).

Reconsideration is requested.

Firstly, the rejection is defective because step (d) of Claim 61 is not taught in the applied art combination.

Step (d) of Claim 61 has two important consequences. One important consequence is that the result of the investigation carried out in step (c) can be properly assessed to reflect a cancer cell. The other important consequence is that it is possible to investigate a second marker (nucleic acid) which is also expressed in non-cancer cells (contrary to Ditkoff, Hoon, Schmitz and Rimm); particularly it is possible in the instant method to determine an increased or decreased presence of the second nucleic acid in a cancer cell relative to a non-cancer cell at a given time (which is necessary because the level of expression of the second nucleic acid may not only vary in cancer cells but also in non-cancer cells).

Secondly, the rejection is defective because it relies on the position that one skilled in the art would expect that using different markers for unenriched body fluid and enriched body fluid would provide increased specificity and sensitivity because Hoon says this occurs when two markers are used for detection in unenriched body fluid, and it is submitted that the conclusion of this position doesn't logically follow.

Consider that detecting one or more mRNAs in a plurality of cells (i.e., in an unenriched body fluid) is problematic because of false positive results, i.e., the mRNA detected does not belong to a cancer cell (see Professor Giesing's declaration submitted on 18 March 2005).

The Office Action points this out for Ditkoff.

It is submitted that one skilled in the art would consider Hoon's suggestion to detect more than one marker in unenriched body fluid would increase the likelihood of obtaining a false positive result in a patient who factually has no disseminated cancer cells. Thus Hoon does not have to provide an improvement compared to Ditkoff.

Schmitz is likewise defective. Where Ditkoff and Hoon obtain a false positive result by using a marker A for detection, the method of Schmitz results in enrichment of non-cancer cells by using a marker A for selective enrichment because the marker A used by Schmitz is found in said non-cancer cells which give rise to said false positive result. Consider also that Schmitz teaches against detection in unenriched body fluid.

While Rimm attempts to avoid false positive results by density-based enrichment (a method which is claimed to work regardless of the source of spread and thus does not require using marker A for enrichment) the use of marker A in Rimm for verification would lead to a false negative result if the enriched cancer cells are dedifferentiated (and thus lack marker A) or if shown to be cancer cells by morphometric analyses would fail to provide information about origin in the cancer cells that are dedifferentiated.

The invention of Claim 61 increases the chance of meaningful determination in all of the above cases.

Consider additionally that an aim of the invention is to establish a risk profile. The applied prior art does not address this purpose. Thus, the prior art cannot be combined to achieve this purpose.

Allowance is requested.

Respectfully submitted,
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Date: November 15, 2005

Case: M-38030-US
B&T Docket No. GIES3003